UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/030,613	01/03/2002	Y Tom Tang	PF-0711 USN	8308

22428 7590 11/26/2004

FOLEY AND LARDNER
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

EXAMINER	
SAIDHA, TEKCHAND	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 11/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	10/030,613	TANG ET AL.	
	Examiner	Art Unit	
	Tekchand Saidha	1652	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 25 October 2004 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☒ The period for reply expires *4* months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1.☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2.☐ The proposed amendment(s) will not be entered because:

(a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

(b) ☐ they raise the issue of new matter (see Note below);

(c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

(d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____.

3.☐ Applicant's reply has overcome the following rejection(s): _____.

4.☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5.☐ The a)☐ affidavit, b)☐ exhibit, or c)☐ request for reconsideration has been considered but does NOT place the application in condition for allowance because: _____.

6.☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7.☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: _____.

Claim(s) objected to: _____.

Claim(s) rejected: *3-7,9,11 and 63-66*.

Claim(s) withdrawn from consideration: *1-2, 10, 13, 16-17, 19, 22, 25, 28 & 61-62*.

8.☐ The drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9.☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10.☐ Other: _____

Advisory Action

1. Applicants' Amendment After-Final filed 10.25.2004 is acknowledged. The present status of the claims is as follows.

2. **Claims 3-7, 9, 11 and 63-66** [SEQ ID NO : 3 encoding SEQ ID NO : 1] are currently pending and under consideration in this Office Action.

3. Claims 8, 12, 14, 15, 18, 20-21, 23-24, 26-27, 29-60 have been canceled by the listing of the claims that replaces all prior versions of the claims, as per the above amendment.

4. Claims 1-2, 10, 13, 16-17, 19, 22, 25, 28 & 61-62 are/remain withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, as per the above amendment.

5. Applicant's arguments filed as per the amendment cited above have been fully considered but they are not deemed to be persuasive and/or because no new arguments have been currently presented. The reasons are discussed following the rejection(s).

6. Any objection or rejection of record which is not expressly repeated in this Office Action has been overcome by Applicant's response and withdrawn.

7. ***Written Description***

Claims **3-7, 9, 11 and 63-66** are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had

possession of the claimed invention. These claims are directed to a genus of DNA (or polynucleotide) molecules with either SEQ ID NO: 3 having the limitation of encoding a protein which is 95% identical to the sequence of SEQ ID NO: 1, with vaguely defined detoxification activity as the function, or a method of making such a protein sequence or DNA sequence which is 95% identical to SEQ ID NO : 3 and encodes a protein with a detoxification .

The specification does not contain any disclosure or description of the structure and function of all DNA sequences that are 95% identical to SEQ ID NO : 3, or DNA that encode polypeptide(s) that 95% identical to SEQ ID NO : 1 or use such a DNA in the method of making polypeptide(s) that 95% identical to SEQ ID NO : 1 (claims **3-7, 9, 11 and 63-66**). Further, the specification as filed does not describe specific assays to measure the various polypeptide sequences having the 'detoxification activity' or which is so evident, as none is described. Assay measuring ß-galactosidase activity of a DETX molecule is described. No detoxification activity was even shown to be associated with the DETX molecule(s). The genus of DNAs that comprise these above DNA molecules is a large variable genus with the potentiality of encoding many different proteins. What compound(s) is being detoxified? No specific assay is described. Therefore, many functionally unrelated DNAs are encompassed within the scope of these claims, including partial DNA sequences. The specification discloses only 2 species as human detoxification proteins (DETX1 and DETX2) of the claimed genus with no defined function known which is

insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Prior Applicants' Arguments:

Applicants argue that because of the degeneracy of the genetic code, a skilled artisan can alter a nucleic acid sequence encoding DETX without changing the encoded amino acid sequences [See specification page 22].

In response, it is pointed out that such a meaning i.e. 'due to degeneracy of the genetic code --- without changing the encoded amino acid sequences' is not reflected in the claim language. It is pointed out that Applicants' arguments are well founded as far as what is disclosed – which are the sequences of SEQ ID NO: 1 and SEQ ID NO: 3. Unfortunately, there are no variants described on page 22 or pages 2 (lines 26-34) and 22 (lines 10-18). Incyte clones are exemplified in Tables 2 & 4. Neither clear cut guidance, nor even a single example is provided as to what regions/motifs/nucleotides of the sequence(s) are modified without impairing the functionality of the DETX protein in order to create a sequence having 95% identity with respect to SEQ ID NO : 1 or 3. Therefore based upon the data provided, i.e. the sequences of SEQ ID Nos. 1 & 3, one skilled in the would recognize, or modify sequences by 10% and still obtain a functional DNA capable of encoding a detoxification protein, for which no clear assay is described and for which no clear functional basis is evident,

written description remains unsupported both in the context of *Vas-cath, Inc. v. Mahurkar,* 19 USPQ2d 1111, 1117 (Fed. Cir.1991) as well as US Patent and Trademark Office's "Guidelines for Examination of Patent Application under the 35 USC Sec. 112, paragraph 1", published January 5, 2001.

It is pointed out that the claims are directed to isolated modified polynucleotide(s), wherein such modifications are neither taught nor described, and wherein such modified or variant polynucleotides may or may not necessarily encode a functional protein. Therefore, the functionality of the claimed polynucleotide is as vital as that of the polypeptide it encodes. Therefore, the written description requirements, as per the Patent and Trademark Office's "Guidelines for Examination of Patent Application under the 35 USC Sec. 112, paragraph 1", published January 5, 2001, are not met.

Applicants further argue that the specification describes an assay that correlates with DETX activity and therefore, can be used to screen sequences that share 90%[now 95%] identity with SE QID NO: 1 or 3 and meet the functional requirement of the presently claimed invention.

An assay if any is not clearly defined. The protein capability with respect to detoxification need to be explored further in terms of what compounds can be detoxified, as none is described.

Applicants' Arguments **(New)**:

Applicants argue that the specification describes both the structure and function of the claimed sequences. Foremost, the claims recite that the

polynucleotides of the present invention encode an amino acid sequence that has at least 95% identity to SEQ ID NO: 1 and has detoxification activity. Furthermore, Table 2 of the present specification discloses potential phosphorylation and glycosylation sites, as well as signature sequences, motifs, and/or domains. Therefore, one of skill in the art would recognize the relevance of these regions and would know how to modify SEQ ID NO: 1 so as to make a sequence that shares at least 95% sequence identity to SEQ ID NO: 1 and has detoxification activity.

In response, and as indicated before it is unclear what is being 'detoxified'. Applicants in response to a 112 (second) rejection, made in the last Office Action, argue that one skill in the art would know what is meant by detoxification activity. For example, Applicants further argue, that the present specification states: 'that detoxification is the metabolic conversion of pharmacologically active, often toxic molecules to less active molecules." The instant specification exemplifies detoxifying enzymes involved in the detoxification of lipid soluble drugs and various metabolites, and enzymes of cytochrome P450 family.

Applicants arguments are considered but not found persuasive, because the ROS detoxifying enzymes exemplified have not been shown to be the functionally similar or related to the Applicants' SEQ ID NO: 1.

Further, Applicants point to Table 2 of the present specification which discloses potential phosphorylation and glycosylation sites, as well as signature

sequences, motifs, and/or domains. In response these potential sites as well as signature sequences, motifs, and/or domains, may well be potential to future research in obtaining and arriving at a probable functionality to the protein in question. However, as per the instant specification no specific function is known or has been assigned to SEQ ID NO: 1, nor would have been obvious to one of skilled in the art to reasonably conclude that the claimed protein would be a specific detoxifying enzyme capable of converting or detoxifying compounds X, Y or Z.

8. Claims **3-7, 9, 11 and 63-66** are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polynucleotide sequence of SEQ ID NO: 3, encoding a human detoxification protein [or DETX1] polypeptide sequence of SEQ ID NO : 1, does not reasonably provide enablement for any polynucleotide having 95% identity to SEQ ID NO: 3 or a polynucleotide encoding a polypeptide having at least 95% sequence identity to the amino acid sequence of SEQ ID NO : 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The scope of the claims does not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polynucleotides broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties,

predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the nucleotide [SEQ ID NO : 3] and encoded amino acid sequence of SEQ ID NO : 1.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications of any DNA with 95% identity to the DETX1 protein of SEQ ID NOS: 1, because the specification does **not** establish: (A) regions of the protein structure which may be modified without effecting DETX1 protein activity; (B) the general tolerance of DETX1 protein to

modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any DETX1 protein residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

This is further supported by Applicants' recent BLAST analysis showing that SEQ ID NO: 1 is 99% identical to the calcineurin inhibitor ZAKI-4 (g21307625) [Cao et al. Biochem. J. 367 : 459-466 (2002)], where an actual showing of the function is evident by experimentation. As can be clearly seen from Applicants' recent BLAST analysis a 1% difference or change in the sequence identity i.e. between ZAKI-4 and DETX1 (EQ ID NO : 1), completely changes the functionality of the polypeptide from being a calcineurin inhibitor to a human detoxification protein. Thus there is high unpredictability associated with respect to modification(s) of the sequence of SEQ ID NO : 1, resulting from modification of the polynucleotide(s) encoding proteins of varying or no function(s).

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of exact nature DETX1 protein encoding DNA (or polynucleotide) having the

desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue in using the modified enzyme in the method claimed. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Applicants' Arguments:

Applicants have clearly failed to address issues raised in the last Office Action. Applicants' present response traverses this ground for rejection, and states that a skilled artisan would know, based upon the teachings in the present specification, how to make and use the inventive DETX protein of the claimed invention.

Once again Applicants' have failed to address the issues raised in the prior Office Action, and the amendment does not overcome the rejection.

Applicants' Arguments (New):

Applicants argue that since DETX activity can be readily assayed by techniques known in the art and in the specification, modifying the claimed sequences to preserve detoxification activity is enabled by the present application.

In response, it is pointed out that a general reference to DETX activity does not in any way impart functionality to the instantly claimed polynucleotide encoding a protein 95% identical to SEQ ID NO: 1 and having DETX activity, because no specific DETX activity has been shown to be actually associated with the sequence of SEQ ID NO: 1. Applicants are invited to point

to such a disclosure in the instant specification, showing, for example, that compound X is detoxified to compound Y by SEQ ID NO: 1. Absent such a disclosure or absent a reasonably enabling disclosure, the instant claims are not enabled.

9. ***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321© may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 3-7, 9, 11 & 63-66 are rejected under the judicially created doctrine of double patenting over claims 1-13 of U. S. Patent No. 6,524,819 since the claims, if allowed, would improperly extend the "right to exclude" already granted in the patent.

The subject matter claimed in the instant application is fully disclosed in the patent and is covered by the patent since the patent and the application [common assignee, different inventors] are claiming common subject matter, as follows: Applicants' Polynucleotide (SEQ ID NO : 3) encoding the polypeptide of SEQ ID NO : 1 is disclosed in the cited patent and is 100% identical, is comprised by the polynucleotide sequence of SEQ ID NO : 1 (or encoding the polypeptide sequence of SEQ ID NO : 2) disclosed in cited USP '819. The reference anticipates the claims.

As per Applicants' request the requirement is held in abeyance until there is indication of allowable subject matter.

10. Claims 3-7, 9, 11 & 63-66 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility.

Applicants disclose a nucleic acid sequences (SEQ ID NO: 3) encoding the amino acid sequence of SEQ ID NO: 1. Based on reasonable sequence homology, the polypeptide of SEQ ID NO: 1 is sought to be a human detoxification protein (DETX) which is a generic asserted utility. human detoxification protein belong to no known family of enzymes or proteins involve

in any specific biological process(es). It is nearly impossible from sequence homology alone to attribute a specific and substantial function for the protein. Even accepting the plausible utility of being a human detoxification protein, one of ordinary skill in the art would not know which compound(s) are detoxified by the polypeptide. The specification does not disclose a specific function of the polypeptides of SEQ ID NO: 1, its relationship to any disease, or any specific real world use. The specification describes generic functions for the protein, nucleic acid, and antibodies. The utility of the variant nucleic acid is said to be associated with encoding defective polypeptides, wherein the variants are associated with disease state, such as the diseases listed on page 45-46. It appears that the main utility of the polypeptide and nucleic acid is to carry out further research to identify the biological function and possible diseases associated with said function. Substantial utility defines a real world use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a real world context of use are not substantial utility. Thus, the claimed invention has no specific or substantial asserted utility.

Applicants' Arguments –

Applicants pointing to specification, page 33, lines 4-32, argue that the specification describes disorder associated with decreased DETX expression and how one would achieve increased DETX expression to treat or prevent such disorders.

As indicated in the Office Action, the specification does not disclose a specific function of the polypeptides of SEQ ID NO: 1, its relationship to any disease, or any specific real world use. Specification on page 33, states that DETX appears to play a role in autoimmune/inflammatory disorders, and cell proliferative disorders, including cancer. In the treatment of disorders associated with increased DETX expression or activity, it is desirable to decrease the expression or activity of DETX. In the treatment of disorders associated with decreased DETX expression or activity, it is desirable to increase the expression or activity of DETX.

The use of phrases such as 'appears' or 'desirable', is further indicative of the non-disclosure of a specific function or its relationship to any disease, or any specific real world use. This is further substantiated by the association of the DETX molecules with a laundry list of disorders, none of which have been characterized or have been shown to be associated with DETX molecules(s) in question. Thus, the claimed invention has no specific or substantial asserted utility.

Applicants new arguments:

Applicants argue that USPTO does not require Applicants to describe the mechanism by which a given compound acts for a showing of utility. As discussed above, the present specification describes the DETX methods and compositions of the present invention can be used to treat or prevent certain disorders.

In response, Applicants' argument is persuasive as far the USPTO requirements for describing the mechanism by which a given compound acts for a showing of utility is concerned. However, no such requirement is made. Applicants are merely to show specific or substantial asserted utility, and such is lacking. Therefore, the rejection is maintained.

Applicants' arguments were considered but not found to be persuasive, for reasons of record.

11. No claim is allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tekchand Saidha (Ph.D.) whose telephone number is (571) 272-0940. The examiner can normally be reached on Monday-Friday from 8:15 am to 4:45 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy, can be reached at (571) 272-0928. The fax phone number for this Group in the Technology Center is 703 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is 571 272-1600.

Tekchand Saidha
Primary Examiner, Art Unit 1652
Recombinant Enzymes, E03A61 Remsen Bld.
400 Dulany Street, Alexandria, VA 22314
Telephone : (571) 272-0940
November 17, 2004